



EFFECTS OF *MONDIA WHITEI* ON THE TEAR FUNCTION OF RABBIT EYES

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Abstract:

Background: Dry eye is a serious problem affecting up to 20% of the world's population. *Mondia whitei*'s rich androgenic properties create an interest in research focused on its efficacy as an alternative and complementary therapy for the treatment and control of the symptoms of dry eye-related diseases associated with androgen deficiency. **Aim:** This study aimed to investigate the effect of *M. whitei* on the quality and quantity of tears in rabbit eyes. **Setting:** This study was carried out at the animal house at Masinde Muliro University of Science and Technology, Kakamega, Kenya. **Materials and methods:** The study adopted an experimental study design with 16 New Zealand rabbits. A simple random sampling technique was used to place the rabbits into 4 groups, each group with 4 rabbits. They were tested for tear function to establish a baseline before administration of Benzalkonium Chloride (BAC) (to induce dry eye) and *M. whitei* extract. Schirmer's test and fluorescein staining were conducted to observe the tear quantity and quality over a period of 6 days after treatment. The data collected was then cleaned and analyzed. **Results:** The researchers found that the average mean during baseline tear quantity measurement for the groups was 26.5mm, during instilling of BAC the mean dropped to 24.0mm and when *M. whitei* was administered the mean rose to 27.94mm, indicating that *M. whitei* greatly improved tear quantity. During baseline tear quality assessment, the average mean for the groups was 0.00 which dropped to 0.94 showing mild staining and when *M. whitei* was administered dropped further to 1.67 indicating that *M. whitei* did not improve the tear quality. **Conclusion and Recommendations:** The researchers recommended that more research be done on *M. whitei* with fewer limitations such as time, to ascertain its effectiveness on tear quality and quantity.

Keywords: dry eye, tear quality, tear quantity, Schirmer's test, fluorescein staining

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1. Introduction

Dry Eye Syndrome (DES) is a condition of the tear film that is caused by a shortage or excessive tear evaporation leading to damage of the interpalpebral ocular surface causing ocular discomfort (Lemp, 1995). It may be a manifestation of serious systemic disease meaning that early detection could be life-saving and patients with dry eye can develop sight-threatening conditions such as bacterial keratitis (Lemp & Chacko, 2000). Dry Eye Syndrome has two major classifications: the first being aqueous-deficient – a condition characterized by deficient tear output from the lacrimal gland, and the second being evaporative dry eye – typically caused by a dysfunction of the meibomian gland resulting in lipid layer insufficiency (Lemp & Marquardt, 1992).

Prevalence studies of DES have been known to differ depending on country or region. A report revealed the prevalence of dry eye to be between 5-50% (Stapleton et al., 2017). A women's health study in the US revealed DES to be a common ocular condition among women, with a 5.7% prevalence among women who are 50 years and less and up to 9.8% among women between 50 and 75 years old (Schaumberg et al., 2003). Another study that compared the gender and age prevalence, found DES to be significantly higher among women (24.7%) than men (18.0%) while the most affected age ranged between 55-64 years (Caffery et al., 2019). In a long-term incidence study of dry eye among older citizens, a 21.6% incidence rate of DES was reported among those aged between 45-92 years over 10 years (Moss et al., 2000). In Nigeria, up to 19.2% prevalence of DES was recorded in a hospital-based survey (Onwubiko et al., 2014), while in South Africa, black participants (59%) and female participants (76%) had a higher prevalence of dry eye than Indian participants (Castelyn et al., 2015).

Mondia whitei (*M. whitei*), or *Mondia whytei*, also known as African ginger or tonic root is a member of the Apocynaceae family that is very popular in Africa for its medicinal, cultural, and nutritional uses. Some of the ailments it has been used to treat are stress, general body aches, eating disorders, and sexual dysfunctions (Aremu et al., 2011). It is a climber with large leaves and purple flowers that grows up to 6 meters long (Venter et al., 2009). The long tuberous roots spread wide just below the soil surface making them easy to harvest (Van Wyk, 2011). *M. whitei* can be found in most parts of the continent and is known to survive in varying climatic conditions ranging from swamps to grasslands (Venter et al., 2009). Studies abound that support the use of *M. whitei* as an aphrodisiac (Lampiao, 2009; Martey & He, 2010). Another study tends to support the ability of *M. whitei* to convert cholesterol to androgen (Watcho et al., 2005). The study which was done on male rats fed orally on *M. whitei* extract for 30 days, found the intertesticular cholesterol of the rat to have decreased, while, the serum and tissue total protein, on the other hand, had increased (Watcho, 2005). In addition, another study found a significant motility of human sperm following treatment with an aqueous extract of *M. whitei* (Lampiao et al., 2008). The findings all point to the ability of *M. whitei* to increase the serum level of androgen hormone in the body.

Androgen has several major functions in the human body. First, the hormone is responsible for controlling the growth, differentiating and regulation of lipid production by the sebaceous glands in the body (Thody & Shuster, 1989). Furthermore, in a study where orchietomy was done on rabbits, there was a staggering change in the lipid levels of the rabbits' meibomian glands (Sullivan et al., 2000). These findings support the hypothesis that androgen controls the meibomian gland function. The meibomian gland is a sebaceous gland that produces the lipid layer of the tear film which prevents evaporation of tears and maintains its stability (Schaumberg et al., 2003). It is believed that when there is androgen deficiency, the meibomian gland will also be affected, thus leading to dry eye. First, patients undergoing anti-androgen therapy have been known to develop dry eyes because of altered lipid layer secreted by the meibomian gland (Krenzer et al., 2000). Secondly, women with Complete Androgen Insensitivity Syndrome (CAIS) have twice more dry eye symptoms than controls and are associated with the increased presentation of dry eye signs and altered secretions of the meibomian glands (Cermak et al., 2003; Sullivan et al., 2000). It is believed that extract of *M. whitei* causes an increase in serum androgen level (Aremu et al., 2011). It is further believed that since the extract of *M. whitei* showed some androgenic effects on the quality (motility) of human sperm as well as alter the parameters of the reproductive organs in rats and rabbits, then it may be possible to exact effect on the function of the meibomian glands in persons with DES.

Dry eye syndrome is a growing public health problem as it can lead to visual impairment if not properly managed. This results in reduced work productivity, inability to perform activities of daily living and decreased quality of life, this is a challenge considering it affects people of all races, ages and cultures. There are various treatment options available for management of the condition but there is no permanent cure. In developing countries such as Kenya, where majority of the population lives below poverty line, there is poor access to these treatments as many cannot afford them.

Studies have been conducted on the medicinal effects of *M. whitei* however, there is scarcity of published literature on its effect of the tear film. Understanding the unique pharmacological effects of *M. whitei* on DES will be vital in providing further insight into the development of an effective, economical and a readily available therapeutic solution of DES. Hence, this study investigated the effect of *M. whitei* on the quality and quantity of tears in rabbit eyes

2. Materials and Methods

The study was carried out in the animal house in Masinde Muliro University of Science and Technology (MMUST), Kakamega County, in a standard cage (minimum measurement of 30 inches) x 36 inches (2.5 x 3.0 feet), in a room maintained at temperature of Kakamega town. The researchers used an experimental study design on the sixteen (16) New Zealand rabbits (1.0-2.0 kg). The animals were pre-tested for tear function, treated and then post-tested after 48 and 72 hours of introduction of treatment to ascertain changes that might have resulted from treatment protocol on the rabbit eyes.

The average tear flow rate results of pre-treatment, treatment and post treatment were recorded respectively.

Simple Random sampling technique was used. Sixteen (16) New Zealand Rabbits were randomly distributed into four (4) groups of four (4) animals each.

Table 1 presents a summary of the treatments as administered to the rabbits' eyes during the length of the study.

Table 1: Summary of the treatments as administered to the rabbits' eyes during the length of the study

No. of days for treatment	0 to day 3	Day 3 to day 6	Day 6 to day 9
Rabbit group A	No treatment	No treatment	No treatment
Rabbit group B	No treatment	BAC treatment	<i>M. whitei</i> treatment
Rabbit group C	No treatment	BAC treatment	BAC + <i>M. whitei</i> treatment
Rabbit group D	No treatment	BAC treatment	BAC treatment

The left eye of each rabbit from Groups B, C and D were topically administered thrice daily with 0.1% Benzalkonium Chloride drops for 6 days. Schirmer's test was carried out on day 3 and 6 to confirm the induction of dry eye in the treated eyes of the rabbits.

To evaluate the quantity of tears, Schirmer's strips (5cm by 35mm) were used without anesthesia and for tear quality, the fluorescein strip was used and graded on a scale of 0-3.

3. Results

In this study, ocular parameters for different observations following 9 days of treatment manipulations – baseline findings, induction of BAC and induction of *M. whitei* – are presented below. Tear quality was graded on a scale of 0-3 (based on the level of fluorescein staining) while tear quantity was presented according to Schirmer's measurements – tear flow rate of 25mm after 5 minutes was considered normal.

3.1 Tear Quantity

Table 2 presents the means \pm SD values and *P* values of the tear quantities of the different rabbit groups presenting on different days of the experiment.

Table 2: Means \pm SD values and *P* values of the tear quantities of the different rabbit groups presenting on different days of the experiment

Days of treatment	0 to day 3	Day 4 to day 6	Day 7 to day 9
Rabbit group A	26.0 \pm 0.25mm	26.0 \pm 1.50mm	25.8 \pm 1.95mm
Rabbit group B	26.4 \pm 0.29mm	25.3 \pm 4.78mm	31.0 \pm 0.90mm
Rabbit group C	26.5 \pm 0.43mm	21.0 \pm 6.81mm	30.0 \pm 1.32mm
Rabbit group D	26.4 \pm 0.39mm	23.6 \pm 5.62mm	25.9 \pm 3.29mm
<i>P</i> value	0.377	0.646	0.022

$\alpha = 0.05$

From the table above, it is easy to deduce that the tear quantity of the control group (group A) remained considerably high throughout the length of the study while that of group D (only treated with BAC) was low the entire time.

3.2 Tear Quality

Table 3 is a summary of the means (means \pm SD) and *P* values of the recorded grading levels of the level of fluorescein staining of the rabbit eyes.

Table 3: Summary of the means (means \pm SD) and *P* values of the recorded grading levels of the level of fluorescein staining of the rabbit eyes

Days of treatment	0 to day 3	Day 4 to day 6	Day 7 to day 9
Rabbit group A	0.0 \pm 0.00	0.08 \pm 0.14	0.00 \pm 0.00
Rabbit group B	0.0 \pm 0.00	0.67 \pm 0.58	1.33 \pm 0.57
Rabbit group C	0.0 \pm 0.00	1.33 \pm 1.15	2.33 \pm 0.57
Rabbit group D	0.0 \pm 0.00	1.67 \pm 1.53	3.00 \pm 0.00
<i>P</i> value	0.00	0.291	0.000

$\alpha=0.05$

Group A constantly recorded the least mean while group D had the highest mean because of deep staining indication poor tear quality.

4. Discussion

4.1 Tear Quantity

From observation of the tables, it can be deduced that the baseline means were fairly similar after the first 3 days because production of tears by the lacrymal glands had not been interfered with by administration of BAC. Upon the instillation of Benzalkonium Chloride, group A's mean remained fairly the same. The mean of group B, C and D dropped. Clinical studies have shown that preservative agents can cause dose-dependent toxic effects that compromise tear film stability and can cause damage to cornea and conjunctiva. Considerable evidence shows BAC's disruptive effect on the tear film. The preservative has a detergent effect on the lipid layer of the tear film. This reduces the lipid layer's stability and causes excessive evaporation, which results in increased ocular dryness (Rosin & Bell, 2013). Considering means between groups, the difference between A and B was thought to be a result of lack of a dry eye causing agent in group A. The absence of BAC instillation in group A means that the tear function was not affected. The lacrymal glands produced tears as they normally would unlike in group B where the tear film was disrupted by BAC. This applies in the differences between the mean of group A and groups C and D as well.

The noticeable difference between the means of groups B and C was possibly because of the already low mean of baseline tear quantity for group C. Since its mean quantity was already low from the beginning of the clinical trials, it's likely that it means would remain low throughout the study. Also, any discrepancies in the instillation of BAC in group C could have resulted in the reduced mean. Possibly, slightly increased

amounts of BAC were put into the rabbit eyes in group C thereby causing reduced production of tears thus lowering the mean. The mean of group D was higher than that of group C but closer to that of group B possibly due to several reasons such as correct instillation of amounts of Benzalkonium Chloride.

After 3 days, instillation of *M. whitei* was begun in groups B and C. Nothing was put into the eyes of group A yet its mean slightly decreased. The researchers tried to explain this by considering internal factors of the rabbit bodies such as hormone production changes, the changes in diet or environmental factors such as wind. Either of this could have caused the slight reduction in tear production in the rabbits in group A. Instillation of *M. whitei* was done in group B and the mean increased. This can be explained by considering the androgenic properties of *M. whitei*. According to Watcho & Sokeng (2004), 4 treated groups were administered orally with a single dose of *M. whitei* (400mg/kg) and the controls received a similar amount of distilled water. This was done for several days and then testicular weights were taken of the male rats in both groups and their means deduced. It was observed that the testicular weight of the rats given *M. whitei* was higher than those of the group given distilled water. This works as proof that *M. whitei* has androgenic properties. This helps to explain the increased tear production in group B. In a different research, an aqueous extract of *M. whitei* was administered to human spermatozoa in vitro and motility parameters assessed. *M. whitei* significantly enhanced total motility as well as progressive motility in a time-dependent manner (Lampiao et al., 2008). This can be explained by the fact that human sperm express a functional androgen receptor (Aquila et al., 2007).

In a research from the US that investigated androgen changes in women over age, it was discovered that age affects female androgen production in two mechanisms. With increasing age, the adrenal glands produce progressively less androgens. Also, menopause results in lessened ovarian androgen production. This results in reduced androgen levels in post-menopausal women (Lois et al., 2014). Therefore, *M. whitei*, for its androgenic properties can come highly useful as an alternative therapy for androgen-related tear function anomalies in women of post-menopausal age.

Instilling *M. whitei* in the eyes introduced androgen hormone in to the eyes' lacrimal gland causing increased production of tears thus raising the mean. Also, since the instillation of BAC had been stopped, the effect of *M. whitei* was not counteracted. The average tear quantity in group C animals appreciably increased despite the instilling of both BAC and *M. whitei* together. To this, the researchers thought that it is possible that one unit of BAC induced less effect on tear production compared to the effect of one unit of *M. whitei* in increasing tear production (Table 2). Hence, it possibly exerts relatively enough androgenic effect of tear production to negate the dry eye-inducing effect of BAC. In group D, the average tear quantity was slightly more increased than we observed with animals in Group C. The animals in Group D were consistently administered BAC throughout the duration of the study, which further confirms not only the dry eye-inducing effect of BAC – in terms of tear quality – but most importantly, that the androgenic effects of *M. whitei* may be significantly effective in stabilizing tear quantity.

Therefore, the increased tear quantity observed in animals of Group D may be high due to reflex tearing in response to the detergent effect of BAC (Sullivan et al., 2000).

4.2 Tear Quality

After fluorescein staining of the rabbit eyes to assess the lipid layer for baseline tear quality measurement, all groups recorded the same mean of 0.00 mm which meant there was no staining. At the beginning of the study, no tear affecting agent had been instilled into the eyes. This means that the tear film was healthy and undisrupted. The lipid layer had no breakages so evaporation and drainage of the aqueous layer of the tears was at its minimal. Deductively, the tear film of the rabbits was normal. BAC was instilled in groups B, C, and D for 3 days and fluorescein staining was done again. The mean of group A was fairly close to 0, meaning that there were no breakages in the lipid layers of the rabbit eyes in absence of BAC and *M. whitei* which affect production of tears. In group B, mild staining was observed since there was instillation of BAC. BAC has shown to cause tear film instability through direct interactions with the lipid components of the tear film (Wilcox et al., 2017). From this it can be derived that administration of BAC led to mildly reduced consistency of the lipid layer hence the recorded mean. The mean of group C and D was higher than that of group B. the instillation of *M. whitei* caused slightly more breakages in the lipid layer of the tear films.

After the last 3 days, group A remained at no staining with a mean of 0.0 mm due to the absence of both BAC and *M. whitei*. Group B was continued with *M. whitei* and its mean remained as it was when the eyes were instilled BAC. The implication of this could be that the extent of dry eye caused by the BAC was not helped by *M. whitei*, thus the lipid layer remained inconsistent. This could also mean that the androgenic properties of *M. whitei* have no repairing or healing effect on the lipid layer of tears. Group C had deep staining. BAC had been instilled causing breakage of the lipid layer for the previous days. Instillation of *M. whitei* did not help since its mean increased. This further proves that *M. whitei* has no effect on the lipid layer of the tear film. Group D had very deep staining at the end of the study deduced from the many breakages the lipid layer of rabbits in this group had after they were stained with fluorescein. Since the instillation of BAC was carried on from the beginning to the end of the study, this further justifies its 'detergent' effect on the lipid layer (Sullivan et al., 2000).

5. Conclusion

From the results of this study, *M. whitei* had an effect of significantly increasing the quantity of tears in a BAC-induced dry eye in experimental animals. This may be due to its androgenic property. *M. whitei* has a potential to introduce androgen hormone in the eyes of experimental animals, thus stimulating the tear glands to increase not only aqueous tears but possibly the lipid layer of the tears hence, improving the tear quantity in a BAC-induced dry eye. However, our study has shown that the effect of *M. whitei* may be more useful in tear quantity than quality.

Further studies are recommended in exploring the effect of *M. whitei* in improving tear quality in persons with androgen-deficient tear function since this study has shown it potential as an alternative to orthodox therapy for androgen-related tear quantity deficiency.

Acknowledgement

We would like to express our gratitude to Masinde Muliro University for the opportunity and resources to conduct this experiment. We also acknowledge the support and assistance of our fellow colleagues and supervisors in the course of our study.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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